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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,294	NIELSEN ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,9-22,25-40 and 78-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,9-22,25-40 and 78-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-final Rejection, May 10, 2005, on September 9, 2005. Claims 1, 4, 18, 19, 78, 79 are amended, claim 80 is new. Claims 2, 6-8, 23, 24, 41-77 are cancelled.

Claims 1, 3-5, 9-22, 25-40, 78-80 are under consideration.

Withdrawn Rejections and Objections

Declaration

Applicant's arguments, see page 11 of Applicant's faxed response, filed September 9, 2005, with respect to the Examiner's statement that the priority information is defective because the signed Declaration does not match the priority claimed in the first line of the Specification have been fully considered and are persuasive. Applicant has indicated the amendments made to the instant application (see Applicant's response, faxed page 12). The objection of the Declaration has been withdrawn.

Claim Objections

Applicant's arguments, see page 12 of Applicant's faxed response, filed September 9, 2005, with respect to the objection of claim 18 regarding the use of the trademark name TAXOTERE® have been fully considered and are persuasive. Applicant has amended the claim to use the generic name, paclitaxel." The objection of claim 18 has been withdrawn.

35 U.S.C. § 112, 1st parag.

Applicant's arguments, page 13-14 of Applicant's faxed response, September 9, 2005, with respect to claims 1, 3-5, 9-22, 25-40, 78, 79 have been considered but are moot in view of the new ground(s) of rejection.

35 U.S.C. § 112, 2nd parag.

Applicant's arguments, see page 14 of Applicant's faxed response, filed September 9, 2005, with respect to the rejection of claims 1, 3-5, 9-22, 25-40 have been fully considered and are persuasive. The rejection of claims 1, 3-5, 9-22, 25-40 has been withdrawn.

Regarding the claim amendments of claims 1 and 4, wherein claim 1 is amended to recite, "contacting said cancer cells" and claim 4 is amended to recite "the cells," the rejection has been withdrawn.

Regarding the use of the term "paclitaxel derivative" in claim 3, the Applicant indicates that this term is discussed in the specification at page 19, lines 28 to page 20, line 4 and indicates that paclitaxel derivatives are well known in the art. For example, Patent No. 5,565,478 provides guidance on how to make and use paclitaxel and other taxane analogs.

35 U.S.C. §102 (b)

Applicant's arguments, see page 14-15 of Applicant's faxed response, filed September 9, 2005, with respect to the rejection of claims 1, 3, 9, 10, 20,

and 79 have been fully considered and are persuasive. Applicant has amended the claims. The rejection of claims 1, 3, 9, 10, 20, and 79 has been withdrawn.

35 U.S.C. § 103(a)

Applicant's arguments with respect to claims 1, 3-5, 9-22, 25-40, 78, 79, see pages 15 and 16 of Applicant's faxed response, filed September 9, 2005, have been considered but are moot in view of the new ground(s) of rejection.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 9-22, 25-40, 78-80 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

an *in vitro* method for reducing the size of a tumor comprising mammalian cancer cells deficient in functional p53, said method comprising contacting cancer cells with an expression vectorr comprising a nucleic acid encoding p53 and also contacting said cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that one or more disease characteristic of the cells is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells and

an *in vivo* method for reducing the size of a tumor in a mammal mammalian cancer cells deficient in functional p53, said method comprising contacting cancer cells with an adenoviral vector comprising a nucleic acid encoding p53, and also contacting said cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that growth of said cancer cells is reduced and/or said cancer cells undergo apoptosis,

an *in vivo* method of treating mammalian cancer cells deficient in functional p53, wherein said method comprises administering directly at cancer cells, a DNA vector comprising a nucleic acid sequence encoding p53, and contacting cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that growth said cancer cells is reduced or such that said cancer cells undergo apoptosis

does not reasonably provide enablement for

an *in vivo* method of treating mammalian cancer cells deficient in functional p53, wherein said method comprises contacting cancer cells with p53 tumor suppressor protein or any DNA vector comprising a nucleic acid sequence encoding p53, wherein said vector is administered by any route, e.g. systemically, intraperitoneally, and contacting cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that one or more disease characteristic of the cells is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells and

an *in vivo* method of treating any human head and neck, ovarian, prostate, or mammary cancer cells including those not deficient in p53 in a human, wherein said method comprises contacting cancer cells with any vector comprising a nucleic acid sequence encoding p53, and contacting cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that one disease characteristic of the caner cell is ameliorated.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art,

(7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

With regards to the scope of the claimed invention being drawn to a method of treating mammalian cancer cells, the art at the time of filing teaches that cancer in mouse models do not behave like cancer in human disease. According to Gura, 1997, Science, 278: 1041-1042, immune deficient mice comprising human tumors do not behaving like tumors in humans because they do not spread to other tissues (Gura, page 1041, 2nd col., 3rd parag.). As this applies to the instant invention, while the specification teaches that a variety of cancer cell lines were transplanted into immune deficient mice, nothing in the specification or the art teaches that the cell lines used in mice were good models for metastases, wherein a p53 or p53 encoded DNA or RAN vector is employed. Neither the prior art of record nor the as-filed specification provides any guidance and/or evidence showing that Ad-p53 administered murine model could be reasonably extrapolated to the full breadth of the claimed invention. Further, while drugs tested in these mouse models appear to work in mice, they work poorly in humans. While the specification teaches a reduction in tumor size in the mouse model, no guidance was provided in the art or specification that that there is a good *in vivo* model for metastases, nor does the specification or art provide any guidance that the combination or p53 and paclitaxel would treat metastases in a tumor bearing subject. It should be pointed out that Neilsen et al., 1998, Clinical Cancer Research, 4: 835-846, teach that p53 and paclitaxel

work at points in the cell cycle and trigger cell death (see abstract). Nothing in the art teaches that either p53 or paclitaxel or the combination of the two have any role in controlling cell migration seen in metastases. As such, the claimed method is limited to reduction in tumor size.

With regards to the scope of the claimed invention being drawn to a method of treating human head and neck, ovarian, prostate, or mammary cancer cells in a mammal, Gura teaches that while xenograft mouse models have been used to screen for cancer drugs, the xenograft model has demonstrated to be unreliable because the mouse model do not handle drugs the same way a human would.

With regards to the claimed method using p53 tumor suppressor protein to treat mammalian cancer cells deficient in functional p53, nothing in the art or specification provides any guidance that p53 protein can be added to a culture dish or can be administered *in vivo* for treatment of cancer cells deficient in functional p53. At the time of filing and even today, the art teaches that there is much difficulty in making drugs that directed at intracellular targets. For example, Dietz and Bahr teach that,

> "On the one hand, drugs directed at intracellular target sites need to be sufficiently polar to be easily administered and well-distributed in the organism. On the other hand, such substances also need to be hydrophobic enough to transverse the lipid bilayer of the cell. Thus, many drug leads fail to make it into clinical trials because they do not fulfil those properties. To circumvent problems of bioavailability, substances often need to be extensively modified..., or their formulation needs to be fine-tuned, for example, for substances that exhibt a low solubility in water. Such problems apply not only to chemically synthesized substances, but also to potentially therapeutic proteins as well (Dietz and Bahr, 2004, Molecular and Cellular Neuroscience, 27: 85-131, page 86, 2nd col., under

'Delivery into calls and across the BBB—why Trojan horse trickery is in demand')."

The art teaches that p53 is an intracellular protein (e.g. see Shaulsk et al., 1991, Oncogene, 6: 2055-2065, abstract). However, nothing in the specification or the art provide any guidance for administering p53 protein to cell culture or to a patient. In addition to the issue of crossing the cell membrane, taught by Dietz and Bahr, the art teaches that there are other difficulties in administering proteins to a patient. The art teaches that there are major problems associated with administration of proteins to a patient. One problem is that there is virtual exclusive clearance of the administered protein by the liver. Another problem that there is potential for bio-inactivation of the administered protein by proteolytic enzymes found circulating in the bloodstream. Another problem is that because the protein is not specifically targeted to cells containing deficient enzyme activity, the active enzyme has been administered in quantities much greater than the body needs. This in turn may undesirably increase the chances of developing a hypersensitivity reaction (Allen and DiCioccio, U.S. Patent, 5,433,946, patented July 18, 1995, col. 1, line 48 to col. 2, line 3). As such, because nothing in the art or the specification provides guidance for the steps used to administer p53 protein, an artisan cannot use the claimed for the scope of p53 protein.

With regards to the claimed invention being limited to the mouse model described in the specification, the art teaches that what studies are performed in mice are not necessarily indicative of what happens in other mammals,

particularly since the claimed invention embraces RNA and DNA vectors other than adenoviral vectors. This is crucial because the results shown in a urine model, wherein an adenoviral vector is employed cannot be reproduced in another model, let alone in larger mammals, such as human cancer patients. Further, the art teaches that systemic administration of gene therapy vectors is not predictable. (The Examiner is interpreting the routes listed in claim 33 to involve systemic distribution of gene therapy vectors following intra-pleural cavity, oral, buccal, sublingual, intratracheal, transmucosal, bladder, vaginal, uterine, rectal, or nasal administration, as "local" administration has been listed separately.) Post-filing work by Gonin and Gaillard, 2004, Gene Therapy, 11: S98-S108 teach that during the course of development of gene therapy, an artisan would need to consider what animals to use in a study, the duration of the therapy, and route of delivery. With regards to biodistribution, Goinin and Gaillard teach a difference between mice and other mammals as larger species of animals can be justified for use in studies when addressing problems that cannot find solutions in smaller mammals (such as special administration routes, which cannot be modeled correctly in rodents) (Goinin and Gaillard, S105, 2nd col., 4th parag. to page S106, 1st col., 1st parag.). For example, special routes which are not seen in mice would need to be tested. Goinin and Gaillard teach that there are discrepancies in the results of gene therapy between species or preclinical settings that underscore the importance of the anatomic topography of the vein used for i.v. biodistribution testing. It is not surprising that results from a tail vein injection differ from those of an ear or portal injection, independent of the

species effect (Goinin and Gaillard page S106, 1st col., 4th parag.). Thus, the teachings of Gonin and Galliard indicate that administration of a viral vector to a mouse is not predictable of administration to other mammals and that an artisan cannot predict what results occur following non-localized administration of a gene therapy vector. Therefore, the scope of the claimed invention is limited to direct administration using a DNA vector and to an adenoviral vector that is administered to a tumor.

Note that the art teaches that non-viral vectors suffer from inefficient gene transfer (Somia and Verma, 2000, Nature Review, 1: 91-99, page 91, 1st col., 2nd parag., see also Office Action, May 10, 2005, pages 7-9). Based on this teaching by Somia and Verma, it is unclear how much plasmid comprising a nucleic acid sequence encoding p53 would need to be administered such that an artisan could detect an effect of p53 on cancer cells, nor is it clear whether the plasmid construct drives expression of p53 at therapeutic levels. While the applicant provides post-filing art (Nielsen et al., 1998, Clinical Cancer Research, 4: 835-846) indicating that there was a synergistic effect between p53 and paclitaxel, wherein p53 was provided in an adenoviral vector comprising a nucleic acid sequence encoding p53, Nielsen et al., indicate that it is not completely clear what caused the synergistic effect of paclitaxel and p53, but do indicate the synergy may result from the fact that more tumor cells were transduced with adenoviral vector (Nielsen et al., page 840, under "Paclitaxel Effect on Ad Transduction Rates"). As such, while the synergism may be accounted through an increase in adenoviral transduction, nothing in the specification provides

guidance that non-viral vectors would transfect cancer cells at a higher rate. While Nielsen et al. suggest that paclitaxel may "sensitize" a cancer cell, nothing in the specification or the art indicates what this sensitization is such that an artisan could use plasmid DNA and expect that enough p53 could be expressed in the cancer cell, wherein a non-direct route of administration is employed. As such, the results shown in the working examples and in the cited Nielsen reference are not reasonably reproducible in a mammal or human, wherein the indicated non-enabling embodiments are employed by a skilled artisan.

Regarding the scope of the claimed invention being drawn to a method of treating human head and neck, ovarian, prostate, or mammary cancer cells in a mammal, wherein the method comprises administering to the mammal a p53 tumor suppressor protein or nucleic acid sequence encoding a p53 tumor suppressor protein (see claim 78), the claim broadly encompasses any human head and neck, ovarian, prostate, or mammary cancer cell, including that which is comprised of a functional p53. According to the art, while an adenovirus expression vector was developed for the delivery of wild-type human p53 cDNA to cells, the expression vector induced apoptosis in cancer cells with mutated or deleted p53 but only minimally affected growth of cells containing wild type p53 (Roth and Cristano, 1997, Journal of the National Cancer Institute, 89: 21-39, see page 24, 1st col., 3rd parag.). As such, the claimed invention is not enabled for the full breadth of any human head or neck, ovarian, prostate, or mammary cancer cell.

In view of the lack of guidance, working examples, breadth of the claims, the state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Claim Rejections - 35 USC § 102 or 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 4, 5, 9, 10, 18-22, 25, 26, 28, 31, 32, 33, 37, 38, 78, 79, 80 are newly rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious, over Roth et al., US Patent 5,747,469, patented May 5, 1998.

Roth et al. generally teach inhibition of the cell cycle at the G1 phase by increased levels of the wild-type p53 protein allows more time for DNA repair; if optimal repair is impossible, p53 may trigger programmed cell death. Thus, p53 may contribute to the induction of apoptotic tumor cell death by chemotherapeutic agents. For example, Roth et al. teach that loss of p53 function has been reported to enhance cellular resistance to a variety of chemotherapeutic agents. Roth et al. have show in previous studies that human

non-small cell lung cancer (NSCLC) H358 cells, in which both alleles of p53 are deleted, were resistant to chemotherapeutic drugs, whereas cell line WTH226b, which has endogenous wt-p53 readily showed apoptotic cell death 16 hours after treatment with cisplatin and etoposide. As such, Roth et al. determined, whether the introduction of the wt-p53 gene into H358 cells by an adenoviral vector could increase the cell's sensitivity to the DNA crosslinking agent CDDP *in vitro* and *in vivo* (Roth et al., Example 7, col. 28, lines 11-42).

In the *in vitro* study, Roth et al. teach that H358 cells were transduced by exposure to Ad-p53, an adenoviral vector comprising a nucleic acid sequence encoding p53. Roth et al. teach that continuous exposure of Ad-p53-infected H358 cells to CDDP reduced the cells' viability. Roth et al. teach that sensitivity of p53-transduced H358 cells to CDDP was dose dependent (Roth et al., col. 29, 4th parag.). In the *in vivo* study, Roth et al. teach that following 3 days of direct intratumoral injection of Ad-p53 or intraperitoneal administration of CDDP H358 tumors implanted subcutaneously in nu/nu mice showed a modest slowing of growth. However, if Ad-p53 and CDDP were simultaneously administered, tumors partially regressed and the tumor size remained statistically significantly smaller than those in any of the treatment groups. Further, the growth inhibitory effect was even more pronounced after two treatment cycles. Histological examination revealed a massive destruction of tumor cells in the area where Ad-p53 was injected in mice treated with CDDP (Roth et al., col. 31, lines 42-60).

It is noted that the claimed invention is drawn to a method of treating mammalian cancer cells deficient in functional p53, wherein the mammalian

cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells and to a method of treating human head and neck, ovarian, prostate, or mammary cancer cells in a mammal. Roth et al. teach lung cancer cells deficient in p53. In the event that the claimed method is not identical to those disclosed by Roth et al., it is considered that any differences would be the result of minor variations, wherein such variants would have been obvious over the prior art. Thus, the claimed invention as a whole was at least prima facie obvious over, if not anticipated by the prior art.

Regarding whether an artisan would expect that using human head and neck, ovarian, prostate, or mammary cancer cells in the claimed invention would result in the same results as that taught by Roth et al., the art teaches that adenovirus expression vector developed for delivery of wild-type human p53 cDNA induced apoptosis in cancer cells with mutated or deleted p53 but only minimally affected growth of cells containing wild-type-p53 (Roth and Cristiano, 1997, Journal of the National Cancer Institute, 89: 21-39, page 24, 1st col., 3rd parag.). In addition to this, an artisan, given the general teachings of Roth et al., US Patent 5,747,469, would at least expect that there would have been an additive effect from the treatment with Ad-p53 and a DNA-damaging stimuli. While the Applicant points out (Applicant's response, faxed page 16) that there was an unexpected result demonstrated by Nielsen et al, 1998, wherein the Applicants observed a synergistic effect upon administration of an adenovirus comprising the nucleic acid sequence of p53 and paclitaxol, Roth et al., US Patent 5,747,469, had anticipated that there was going to be an effect resulting

from the treatment of p53 and doxyrubicin (Roth et al., US Patent, 5,747,469, claim 6) and the synergistic or additive effect of administering p53 and doxyrubicin to the cancer cell is inherent to the method described by Roth.

The Applicant indicates that a synergistic effect between adenovirally administered p53 and paclitaxel is seen when the adenoviral vector is administered before paclitaxel (Applicant's faxed response, page 15-16). While Roth et al. do not indicate that the order of administration would result in a synergistic effect, Roth et al. anticipate the claimed invention because Roth et al. teach that the combination of two agents would have a better therapeutic effect than each agent alone, regardless of order. See also claims 35-37 of Roth et al.'s patent.

Regarding the issue of how much adenoviral vector is administered, Roth et al. contemplate that the administered amount is $1x10^5$ to $1x10^{12}$, see claim 16, of Roth et al. patent.

Thus, Roth et al. anticipate claims 1, 3, 4, 5, 9, 10, 18-22, 25, 26, 28, 31, 32, 33, 37, 38, 78, 79, 80.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al., US Patent 5,747,469, patented May 5, 1998.

Roth et al. generally teach inhibition of the cell cycle at the G1 phase by increased levels of the wild-type p53 protein allows more time for DNA repair; if optimal repair is impossible, p53 may trigger programmed cell death. Roth et al. also provide an *in vitro* and an *in vivo* example wherein administration of an adenovirus comprising a nucleic acid encoding p53 was administered with a chemotherapeutic agent, CDDP, and the combination therapy resulted in greater therapeutic effects than either treatment alone (see above, 102/103 rejection for more details). It is noted with regards to the scope of any chemotherapeutic agent, as written in claim 4, Roth et al. teach DNA damaging agents that are used as chemotherapeutic agents (Roth et al., col., 18-19 under "F. DNA Damaging Agents"). These include agents that crosslink DNA, agents that intercalate into DNA, and agents that lead to chromosomal and mitotoic aberrations by affecting nucleic acid synthesis. Roth et al. teach that using these DNA damaging agents are envisaged to eventuate DNA damge leading to a synergistic antineoplastic combination (Roth et al. col. 19, 2nd parag.).

While Roth et al. do not teach administration of an adenovirus comprising a nucleic acid encoding p53 and a taxane and then a further step of administering a chemotherapeutic agent of cisplatin, carboplatin, or navelbine, it would have been obvious to an artisan to administer an adenovirus comprising a nucleic acid encoding p53, a taxane, and another chemotherapeutic agent. Roth et al. teach that H358, non-small lung cancer cells, in which both alleles of p53

are deleted, are resistant to chemotherapeutic drugs. However, when an adenoviral vector comprising a nucleic acid sequence encoding p53 was administered to the cells or to the mouse comprising the tumor, these cells were now responsive to chemotherapy drugs (Roth et al., col. 28, lines 31-38 and Example 8). Adding another chemotherapeutic drug for an additional therapeutic effect would have been obvious.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made use an adenovirus comprising a nucleic acid encoding p53, taxane, and another chemotherapeutic agent.

One having ordinary skill in the art would have been motivated to use an adenovirus comprising a nucleic acid encoding p53, taxane, and another chemotherapeutic agent, in order to obtain better treatment of cancer cells, wherein the cancer cells are deficient in functional p53, than in treatments that comprise only one therapy.

There would have been a reasonable expectation of success given that Roth et al. teach that in order for the chemotherapeutic agent to have an effect, that the cells deficient in functional p53 would need to be treated with an adenovirus vector comprising a nucleic acid sequence encoding p53 so that the chemotherapeutic agents would have an effect. Adding a second chemotherapeutic agent would at least add to the therapeutic effect.

Claims 1, 9 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al., US Patent 5,747,469; patented May 5, 1998, as evidenced by Verma and Somia, 1997, Nature, 389: 239-242.

Roth et al. generally teach inhibition of the cell cycle at the G1 phase by increased levels of the wild-type p53 protein allows more time for DNA repair; if optimal repair is impossible, p53 may trigger programmed cell death. Roth et al. also provide an *in vitro* and an *in vivo* example wherein administration of an adenovirus comprising a nucleic acid encoding p53 was administered with a chemotherapeutic agent, CDDP, and the combination therapy resulted in greater therapeutic effects than either treatment alone (see above, 102/103 rejection for more details).

While Roth et al. do not teach the use of viral vectors other than adenovirus, an artisan would have used other viral vectors as a vehicle of p53 gene delivery and at least expect these other vectors to enter a cell and express p53, whereby expression of p53 reduces the number of tumor cells. It is noted that Roth et al. contemplate that viral vectors other than adenovirus are good vehicles as demonstrated in claims 19-21, and as supported by Verma and Somia who teach that non-viral vectors suffer from poor efficiency of delivery and transient expression of the gene (Verma and Somia, page 239, 3rd col., 2nd parag.), while viruses are better vehicles because they have evolved specific machinery to delivery DNA to cells (Verma and Somai, page 239, 3rd col., 3rd parag.).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made use viral vectors other than an adenovirus as a vehicle to deliver the p53 gene directly to tumor cells.

One having ordinary skill in the art would have been motivated to use other viral vectors as a vehicle for delivering the p53 gene because viral vectors are better gene delivery vehicles than non-viral vectors.

There would have been a reasonable expectation of success given that Roth et al., as supported by Verma and Somia, contemplate that other viral vectors are viable vehicles used to deliver a gene of interest directly at cells of choice.

Claims 1, 3, 4, 5, 9-12, 15-22, 25, 26, 28, 31, 32, 33, 37, 38, 78, 79, 80 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al., US Patent 5,747,469, patented May 5, 1998, in view of Moojoo et al., 1996, Oncogene, 12: 1617-1623, and as evidenced by Wills et al., 1994, Human Gene Therapy, 5: 1079-1088.

Roth et al. generally teach inhibition of the cell cycle at the G1 phase by increased levels of the wild-type p53 protein allows more time for DNA repair; if optimal repair is impossible, p53 may trigger programmed cell death. Roth et al. also provide an *in vitro* and an *in vivo* example wherein administration of an adenovirus comprising a nucleic acid encoding p53 was administered with a chemotherapeutic agent, CDDP, and the combination therapy resulted in greater

therapeutic effects than either treatment alone (see above, 102/103 rejection for more details).

While Roth et al. do not teach that the adenoviral construct used in their examples was ACN53, Mujoo et al. teach a method wherein ACN53 was administered i.p. in mice comprising SK-OV-3 cancer cells. Mujoo et al. teach that their study is the first example of i.p. introduction of an adenoviral vector and that i.p. injection of ACN53 demonstrated a two to three-fold increase in the survival of 40% animals compared with those injected with PBS or ACN (Mujoo et al., page 1621, 2nd col., 2nd parag.). According to Mujoo et al., the ACN53 vector was obtained from Wills et al., 1994 (Mujoo et al., page 1617, 2nd col., 4th parag.). Wills et al. teach that adenovirus comprising a nucleic acid sequence encoding p53 was constructed by replacing a portion of the E1a and E1b region of the adenovirus type 5 with p53 cDNA under the control of either Ad2MLP or CMV promoter. In additional modifications, the E1b sequence has been deleted to created the protein IX-deleted constructs ACN53 (Wills et al, page 1080, Figure 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to administer ACN53 intraperitoneally to a mouse model comprising cancer cells, wherein the cancer cells are deficient in functional p53, and to also administer to the mice a chemotherapeutic agent to reduce tumor size, in the method described by Roth et al.

One having ordinary skill in the art would have been motivated to administer ACN53 I.P. and a chemotherapeutic agent to a mouse model, as Mujoo et al. demonstrate that ACN53 can be administered I.P. and that Roth et al. teach that administration of adenovirus p53 to cancer cells that lack functional p53 would be a way of making these cancer cells more responsive to chemotherapy.

There would have been a reasonable expectation of success given the results of Mujoo et al. for teaching that ACN53 can be administered I.P. and for Roth et al. for teaching that cancer cells lacking functional p53 is more responsive to chemotherapy when provided with an adenoviral construct comprising a nucleic acid encoding p53.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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